REMARKS/ARGUMENTS

As discussed with the Examiner on April 17, 2006, this Reply and Amendment is intended to supplement and replace the previous amendment submitted on April 10, 2006. The major difference between these responses is that (1) the claims have been amended to specify that the biological sample contains albumin, and that the electrophoretic mobility of albumin is reduced, and (2) comments are included associated with these amendments.

This amendment is in response to the Final Rejection filed April 10, 2006. Entry of the foregoing and favorable reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §§ 1.112 and 1.116, and in light of the remarks which follow, is respectfully requested. Applicants submit that the amendments proffered hereby place the application in condition for allowance and do not require a new search. At the very least, such amendments will reduce the number of issues on appeal. Therefore, entry of the amendments appears to be fully proper under 37 C.F.R. § 1.116.

By the present amendment, claims 1, 20, 21, have been amended to correct certain typographical errors and/or further clarify the present invention. In particular, claims 1, 20, and 21 have been amended to clarify that the electrophoretic mobility of albumin is reduced. Support for this particular amendment appears at least on page 3, lines 7 to 12. Applicants submit that no new matter has been added via this amendment.

Claim Rejections - 35 U.S.C. § 112

Claim 33 has been objected to as improper, and was also rejected under 35 U.S.C. § 112, first paragraph. Again, claim 33 has been cancelled rendering these issues moot with respect thereto.

Claims 20, 24, 25, 27 to 30 and 33 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. With respect to claim 20, the Examiner has stated that "it is not clear what the at least one protein constituent is separated from if it is the only thing that is positively recited as passed into the capillary." Claim 20 has been amended to delete the terminology "at least one", clarifying that more than one protein is present in the sample for separation.

In connection with claim 24, and claims 25, 27 and 30 which depend therefrom, the Examiner stated that "it is not clear what is meant by 'in a liquid support and at least one buffer and additive.'" Claim 24 has been amended to "in a liquid support, at least one buffer and an additive . . . ." In view of these amendments, Applicants submit that the claims are definite. Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 103

Lauer et al. In View Of Karger et al.

Claims 1, 2, 5, 7 to 10, 12 to 21, 23 and 34 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Lauer *et al.* in view of Karger *et al.* (U.S. Patent 4,778,909). For the following reasons, however, this rejection is respectfully traversed.

Lauer *et al.* disclose examples of protein separation by applying a repulsion principle by adjusting the pH of solutions to values where both protein and the wall of the fused

silica capillary have net negative charges. Due to this negative charge, the proteins should be repelled from the silica capillary wall increasing the chances for proper separation of the proteins by capillary electrophoresis.

In this regard the buffer systems set forth in Table II were used to decrease the conductivities of the bulk fluids as described at page 167, last column, last full paragraph. There is no suggestion that these buffers can be used to reduce the mobility of albumin to enhance separation.

Furthermore, all of the proteins referred to in Table I of Lauer *et al.* are not from a human serum sample. Rather, the samples used in Lauer *et al.* were purchased samples from Sigma of non-human origin. (Page 167, first sentence under "Reagents"). Furthermore, the proteins referred to in said Table I have a weight of between 14 and 77kDa. To the contrary, the immunoglobulins, which are of particular interest according to the present invention process, have weights between 150 and 900kDa. It should furthermore again be noted that even if molecular weight and/or isoelectric points are similar, other properties, and amongst them electrophoretical properties can be rather different and cannot be predicted.

Moreover, Lauer *et al.* fails to suggest that this process can be applied to clinical samples. In fact, the skilled artisan when reading this reference as a whole would conclude the same as the authors did in the last paragraph of this paper, which states the following:

"The remaining problems in CZE, such as specific wall adsorption, conductivity gradients within the sample zones and adequate detection, still have to be solved before attempts to improve instrument design can be successful."

Indeed, in Lauer *et al.*, many of the proteins deteriorated under the electrophoresis conditions or the electropherograms showed severe broadening and tailing.

Absorption to the capillary wall remained a problem with conalbumin. Therefore, it is doubtful whether a skilled artisan would use the method of Lauer *et al.* for clinical analysis of human biological samples.

The secondary reference of Karger *et al.*, U.S. Patent 4,778,909 discloses trifunctional silyl ethers of the general formula (RO)3Si-(CH2)m-0-(CH2CH2O)n-(CH2)p-R' where R is an alkyl containing from one to five carbons, m is an integer from 2 to 5, n is an integer from 1 to 5, p is an integer from 0 to 10 and R' is methyl or phenyl possibly substituted by one or more substituents such as hydrogen, lower alkyl, alkoxy, nitro, amino, amido, cyano, ester or halogen. These organosilanes can be bonded to yield stable chromatographic supports for use in hydrophobic interaction chromatography and size exclusion chromatography.

Karger *et al.* has nothing to do with capillary electrophoresis. Indeed, a person skilled in the art would have no motivation to combine these references, since they entail two totally different separation techniques; *i.e.*, there is no electric current used in the methods of Karger *et al.* and the proteins are not eluted off columns in capillary electrophoresis.

As stated by the Federal Circuit in *C.R. Bard Inc. v. M3 Systems, Inc.* 157 F. 3d 1340, 1352, 48 USPQ2d 1225, 1231-32 (Fed. Cir. 1998): a showing of a suggestion, teaching or motivation to combine prior art references is an essential component of an obviousness holding. Applicants submit that there is simply no motivation to combine Lauer *et al.* with Karger *et al.*

Moreover, the Examiner relies upon the disclosure of Karger *et al.* for showing that human transferrin, *i.e.*, human ß1-globulin, which is a serum protein has a pI of 5.0 and a molecular weight of 77,000, is in the range of the proteins in

Table I of Lauer *et al.* However, as taught in Lauer *et al.*, 75% of reported proteins have pI values above 4 and many of these proteins would have a molecular weight of between 13,000 and 77,000 and thus be encompassed in Table I. Besides, the samples, like Lauer *et al.* are not human biological samples, but merely proteins, which were chromatographed in Karger *et al.*

Applicants submit that the Examiner has not read the secondary reference as a whole, as described above, but has only focused on a single teaching in Karger *et al.*, which is human ß1-globulin. This appears to be hindsight reconstruction.

As set forth in *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the invention."

Thus, in view of the above, Applicants submit that the presently claimed invention is not obvious in view of Lauer *et al* and Karger *et al.* Therefore, withdrawal of this rejection is respectfully requested.

Lauer et al. In View Of Karger et al. And Ohmura et al.

Claim 22 has been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Lauer *et al.* in view of Karger *et al.* (U.S. Patent 4,778,909) and further in view of Ohmura *et al.* (U.S. Patent 5,521,287). For the following reasons, however, this rejection is respectfully traversed.

Lauer *et al.* and Karger *et al.* were discussed extensively above. The same arguments are incorporated herein to avoid repetition.

Ohmura *et al.* (U.S. Patent 5,521,287) provides a process for producing recombinant human serum albumin by culturing a host expressing human serum albumin filtering through ultrafiltration membranes, heat-treating the filtrate, acid-treating the heated filtrate, ultrafiltering the heat treated sample, cation-ion exchanging a filtrate with a specific salt concentration, subjecting a filtrate to hydrophobic chromatography and anion exchanging the eluent to recover the purified human serum albumin.

Ohmura *et al.* does not teach or disclose anything about capillary electrophoresis nor their buffering systems. According to Ohmura, sodium salts are used to precipitate albumin. Therefore, the Applicants submit that there would be no motivation to combine Ohmura *et al.* with Lauer *et al.* and Karger *et al.*

Moreover, the Examiner cites one paragraph from this reference, which is the paragraph bridging columns 7 and 8 and relies on this paragraph as disclosing that sodium sulphate can be substituted for the KCl buffer of Lauer *et al.* However, the procedure in Ohmura *et al.* cited by the Examiner is a quote from the process in which the HSA has been salted out, the protein recuperated and dissolved in an appropriate buffer solution so that the HSA can be further purified either by hydrophobic chromatography or an anion exchange treatment step. This patent does not suggest nor even describe that such a buffer can be used in capillary electrophoresis. Rather this buffer is solely used in protein purification to maintain a pure and active form of the protein.

The combination of these references fails to render present claim 22 obvious, since none of these references alone or in combination suggest a method for separating protein constituents in a human biological sample. Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Keo et al.

Claims 1, 4, 5, 7 to 10, 12 to 21, 23 and 34 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Keo *et al.* (U.S. Patent 5,599,433). For the following reasons, however, this rejection is respectfully traversed.

Keo *et al.* disclose a capillary electrophoresis method to separate glycated hemoglobins or glycohemoglobins. Keo *et al.* fail to disclose or suggest to use their buffer composition in any other clinical analysis. Indeed, the only analysis that Keo *et al.* disclose is for the analysis of glycoproteins and specifically for glycohemoglobins. There is simply no suggestion that their buffer system can be used for any other protein analysis using capillary electrophoresis.

Indeed, the patent of Keo *et al.* is strictly limited to using the buffer system for facilitating glycoproteins such as Hb A1c from other sample constituents as clearly indicated at column 5, lines 18 to 21, where the following is stated:

> The buffer of the present invention has at least four elements that facilitate the separation of glycoproteins such as Hb A1c from other sample constituents. These include water, a sugar complexing compound, a zwitterionic compound that has a pKa of from about 9 to about 12 and a base compound for adjusting the pH.

Therefore, it would be clear to the skilled artisan from the above paragraph that there is only one application for the buffer system described in Keo *et al.*; *i.e.*, to separate

Hb A1c from the other proteins in the sample.

Keo *et al.* does not disclose that their buffer system can be used in any other method. Therefore, a person skilled in the art would not have used the buffer system in the present invention to separate albumin, α1-globulin, α2-globulin, ß-globulin, (ß1-globulin, ß2-globulin) and γ-globulin, since there is simply no disclosure of this in Keo *et al.*

Moreover, Keo *et al.* fail to disclose that their additive can, in fact, reduce the mobility of albumin compared with that of the other proteins in the sample. Thus, Applicants submit that the presently claimed invention is not obvious in view of Keo *et al.*

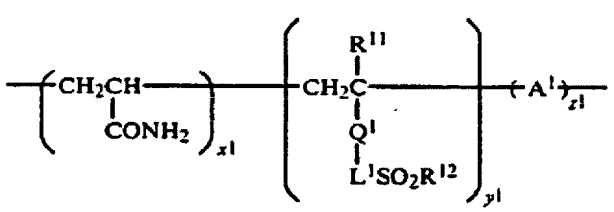
Therefore, in view of all of the above, withdrawal of this rejection is respectfully requested.

Ogawa et al.

Claim 24 has been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Ogawa *et al.* (U.S. Patent 4,769,408). For the following reasons, however, this rejection is respectfully traversed.

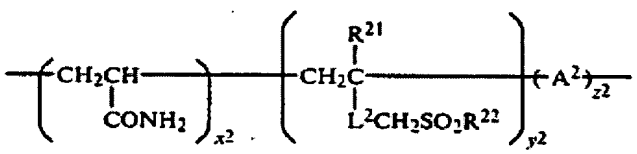
Ogawa *et al.* (U.S. Patent 4,769,408) discloses a medium for electrophoresis in the form of an aqueous gel, which can be prepared in the presence of oxygen. As disclosed at Col.2, l.19 to Col.3, l.25, the gel comprises an acylamide copolymer having the following repeat units:

(1) a repeating unit having the formula(1):



in which R^{11} is the hydrogen atom or an alkyl group containing 1-6 carbon atoms; Q^1 is -COO-, -CON(R^{11})- or an arylene group containing 6-10 carbon atoms; L^1 is a divalent group containing at least one linkage selected from the group consisting of -COO- and -CON(R^{11}) and containing 3-15 carbon atoms, or a divalent group consisting at least one linkage selected from the group consisting of -O-, -N(R^{11})-, -CO-, -SO-, -SO_2-, -SO3-, -SO_2N(R^{11})-, -N(R^{11})CON(R^{11})- and -N(R^{11})COO-, and containing 1-12 carbon atoms, in which R^{11} has the same meaning as defined above; R^{12} is -CH=CH_2 or -$CH_2CH_2X^1$, in which X^1 is a substituent replaceable with a nucleophilic group or releasable in the form of HX^1 by a base; A^1 is a divalent group derived from an ethylenic unsaturated monomer copolymerizable with monomers forming other unit portions; and x^1 and y^1 both representing molar percents range from 50 to 99, and from 1 to 50, respectively, and z^1 represents the remaining molar percent including 0;

(2) a repeating unit having the formula (2):

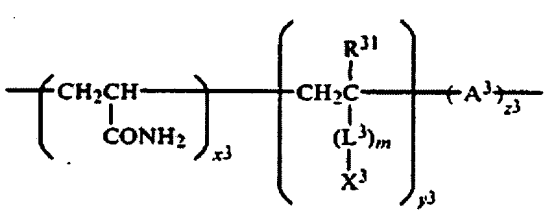


(2)

in which R^{21} is the hydrogen atom or an alkyl group containing 1-6 carbon atoms; R^{22} is -CH=CH_2 or -$CH_2CH_2X^2$, in which X^2 is a substituent replaceable with a nucleophilic group or releasable in the form of HX^2 by a base; L^2 is a divalent group selected from the group consisting of an alkylene group consisting 1-6 carbon atoms, an arylene group containing 6-12 carbon atoms, -COZ^2-, and -COZ^2R^{23}-, in which R^{23} is an alkylene group containing 1-6 carbon atoms, or an arylene group containing 6-12 carbon atoms, and Z^2 is the oxygen atom or NH; A^2

is a divalent group derived from an ethylenic unsaturated monomer copolymerizable with monomers forming other unit portions; and x^2 and y^2 both representing molar percents range from 50 to 99, and from 1 to 50, respectively, and z^2 represents the remaining molar percent including 0; and

(3) a repeating unit having the formula (3):



(3)

in which R^{31} is the hydrogen atom or an alkyl group containing 1-6 carbon atoms; L^3 is a divalent linkage group containing 1-20 carbon atoms; X^3 is an active ester; A^3 is a divalent group derived from an ethylenic unsaturated monomer copolymerizable with monomers forming other unit portions; x^3 and y^3 both representing molar percents range from 50 to 99, and from 1 to 50, respectively, and z^3 represents the remaining molar percent including 0; and m is 0 or 1.

This gel is used in gel electrophoresis and not capillary electrophoresis. In fact there is no mention of capillary electrophoresis throughout this patent. Ogawa *et al.* teach at column 13 lines 34 to 38 that the anionic surfactant is contained in a gel-forming solution. There is no suggestion in this reference that this solution can be used alone, and especially that this anionic surfactant can be suited for use in capillary electrophoresis.

Indeed, the Examiner's choice of only focusing on the buffer solution and not the invention as whole as taught in Ogawa *et al.* could only be made through hindsight by the Examiner. As stated in *Sensonics, Inc. v. Aerosonic Corp.*,

81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996) by the Federal Circuit: "To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction-an illogical and inappropriate process by which to determine patentability."

In view of the above, Applicants submit that Claim 24 is not obvious in view of the fact that the skilled artisan would not use the particular buffer described therein for capillary electrophoresis. Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Bellon et al., In View Of Keyes and Bloebaum et al.

Claims 24, 25 and 27 to 30 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Bellon *et al.* (U.S. Patent 5,928,484) in view of Keyes (U.S. Patent 4,714,677) and Bloebaum *et al.* (U.S. Patent 4,872,865). For the following reasons, however, this rejection is respectfully traversed.

Bellon *et al.* relates to the separation of Lp(a) and various lipoproteins contained in a sample by means of standard *gel electrophoresis* in which the electrophoretic mobility with respect to Lp(a) is modified differentially with respect to those of other lipoproteins in a sample. This modification is performed by either modifying the gel or the sample with agents which are selected from a cation or cationic complex, a molecule having a hydrophobic moiety and is negatively charged or a neutral surfactant. Bellon *et al.* fails to teach the range of the pH in their buffer. Tris is known to buffer at a pH of 7.5 to 9.

The Examiner deems that column 5 lines 37 to 45 disclose a pH of 9. While this may be true, this paragraph does not refer to any buffering purpose, but to the occurrence of the

precipitation. It refers to the selected cations or cationic complexes, the hydroxides of which are not precipitated or partially precipitated at a pH of about 8 to 9. This paragraph does not refer to the Tris buffer as having a pH of about 9, nor does it refer to the hydrophobic moiety, which is negatively charged.

Moreover, as stated at column 8, lines 7 to 12, the gels are used "in the area of electrophoresis, in particular agarose, polyacrylamide or cellulose acetate gels." Note that there is no reference to capillary electrophoresis either at this column or throughout the entire patent.

The secondary references of Keyes and Bloebaum do not remedy the deficiencies of the primary references. Keyes discloses a process for chemically modifying a natural protein to provide the protein with activity of a selected enzyme. The modification is carried out by partially denaturing the protein, contacting the partially denatured protein with an immobilized enzyme inhibitor of the selected enzyme, crosslinking the protein in the presence of the inhibitor and recovering the modified protein. Applicants submit that Keyes cannot be combined with the Bellon reference, since it has nothing to do with electrophoresis, let alone capillary electrophoresis.

Bloebaum *et al.* disclose a physiologically conforming solution for use in arthroscopic surgery in order to reduce the risk of swelling and injury of the synovial tissues. Applicants submit that this reference has nothing to due with electrophoresis, let alone capillary electrophoresis.

The combination of references fails to render the present invention obvious since none of these references teach or suggest capillary electrophoresis. Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claim Rejections - Double Patenting

Claims 1, 2, 4, 5, 7-25, 27-30, and 33-35 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 8-28 and 30 of co-pending U.S. Application No. 10/052,601. Applicants acknowledge that this rejection is provisional and requests that this rejection be held in abeyance until one of these patent applications is allowed.

Final Remarks

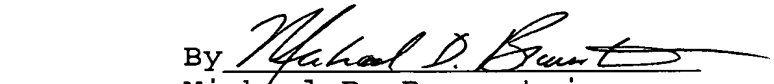
In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: April 21, 2006

Respectfully submitted,

By 

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